## II. REMARKS

**Formal Matters**

Claims 1, 3-9, 11-16, and 20-26 are pending after entry of the amendments set forth herein.

Claims 1-3, 10, 12-19, and 26 were examined and were rejected. Claims 4-9, 11, and 20-25 were withdrawn from consideration.

Claims 1 and 26 are amended. The amendments to claims 1 and 26 were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. Support for the amendments to claims 1 and 26 is found in claim 2 as originally filed, and throughout the specification, in particular at the following exemplary locations: page 13, lines 16-31. Accordingly, no new matter is added by these amendments.

Claims 2, 10, and 17-19 are canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claims. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Rejections under 35 U.S.C.§112, first paragraph

Claims 1-3, 10, 12-19, and 26 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking adequate written description. Claims 1-3, 10, 12-19, and 26 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking enablement.

Written description

The Office Action stated that the instant disclosure fails to provide a representative number of species to describe the broad genus of epidermal growth factor receptor (EGF-R) antagonists that bind the EGF-R. Applicants respectfully traverse the rejection.

As discussed in the amendment, filed on April 23, 2002 and responsive to the January 2, 2002 Office Action, the specification provides ample description of EGF-R antagonists. Specification, page 7, line 21 to page 8, line 23. Many of the EGF-R antagonists discussed in the specification are known to those skilled in the art. The general classes of EGF-R antagonists described in the specification include

tyrosine kinase inhibitors, antibodies that bind a factor that stimulates EGF or EGF-R production, e.g., an antibody to TGF-α.

The specification provides working examples of at least three different EGF-R antagonists: two different tyrosine kinase inhibitors, as well as an antibody to TGF-α. For example, the specification provides working examples that BIBX1522, a tyrosine kinase inhibitor that is an EGF-R antagonist, inhibits MUC5AC production in cultured cells *in vitro* and inhibits mucus hypersecretion *in vivo*. Specification, e.g., Example 1. The specification further provides a working example showing that AG1478, another tyrosine kinase inhibitor that is an EGF-R antagonist, prevented MUC5AC synthesis induced by an activator of EGF-R, and inhibited EGF-R phosphorylation. Specification, e.g., Example 2. AG1478 and BIBX1522 inhibit goblet cell hyperplasia. The specification further provides a working example showing that a TGF-α neutralizing antibody reduced stimulation of the EGF-R and reduced production of goblet cells. Specification, e.g., Example 3.

In view of the above remarks, as well as further remarks made in the amendment, filed on April 23, 2002 and responsive to the January 2, 2002 Office Action, the specification provides ample written description.

Nevertheless, and solely in the interest of expediting prosecution, claims 1, 17, and 26 are amended to recite "wherein the EGF-R antagonist is a tyrosine kinase inhibitor selective for EGF-R." As discussed above, the specification provides ample written description, including working examples, of EGF-R antagonists that are tyrosine kinase inhibitors selective for EGF-R. Accordingly, claims 1, 17, and 26 meet the written description requirement of 35 U.S.C.§112, first paragraph.

Enablement

The final Office Action stated that the claims were rejected for reasons of record in the January 2, 2002 Office Action. The January 2, 2002 Office Action stated that the specification is not enabling for methods of reducing goblet cell hyperplasia in an individual's airways or treating nasal polyps comprising the administration of any EGF-R antagonist via any mode of administration. Applicants respectfully traverse the rejection..

*EGF-R antagonists*

As discussed above, the specification provides ample description of a number of EGF-R antagonists. The specification provides ample description, including working examples, of how to determine whether a given EGF-R antagonist will function to reduce goblet cell hyperplasia. Furthermore, the specification provides **working examples** of *in vitro* and *in vivo* inhibition of mucin expression and airway mucus hypersecretion (and therefore reducing goblet cell hyperplasia) using BIBX1522, an EGF-R tyrosine kinase inhibitor. The specification also provides working examples of two additional EGF-R antagonists. The specification further provides a working example showing that AG1478, another tyrosine kinase inhibitor that is an EGF-R antagonist, prevented MUC5AC synthesis induced by an activator of EGF-R, and inhibited EGF-R phosphorylation. Specification, e.g., Example 2. The specification further provides a working example showing that a TGF-α neutralizing antibody reduced stimulation of the EGF-R and reduced production of goblet cells. Specification, e.g., Example 3.

Thus, the specification provides three working examples of EGF-R antagonists that are efficacious in reducing goblet cell hyperplasia.

Nevertheless, and solely in the interest of expediting prosecution, claims 1, 17, and 26 are amended to recite "wherein the EGF-R antagonist is a tyrosine kinase inhibitor selective for EGF-R." As discussed above, the specification provides guidance, including working examples, for carrying out a method of reducing goblet cell hyperplasia, and for carrying out a method of treating nasal polyps, comprising administering EGF-R antagonists that are tyrosine kinase inhibitors selective for EGF-R. Accordingly, claims 1, 17, and 26 meet the enablement requirement of 35 U.S.C.§112, first paragraph.

*Route of administration*

The January 2, 2002 Office Action stated that the specification is not enabling because practice of the invention would require the *de novo* determination of accessible target sites, modes of delivery, and formulations to target appropriate cells and/or tissues. However, in reducing hypersecretion of mucus in the lungs, the target cell population is in the airways. Thus, there is no need to determine accessibility of target sites, because such is already known. Furthermore, Applicants showed that systemic delivery of BIBX1522 reduces airway goblet cell hyperplasia. Thus, those skilled in the art would reasonably expect that the same EGF-R antagonist or other EGF-R antagonists, when

administered by other routes, e.g., via inhalation, would be efficacious, because administration by inhalation is administration directly at the site of the target cells.

Intratracheal instillation is a well-accepted model for delivery of a drug or other substance into the airways, and as such is a model of delivery by inhalation. Thus, a showing of activity of a given drug by intratracheal instillation is enabling for delivery by inhalation.

Applicants showed that delivery of an EGF-R antagonist directly into the airways, by intratracheal instillation, reduces airway mucus hypersecretion (and therefore reduces goblet cell hyperplasia). When a drug is administered by intratracheal instillation, the site of the drug's action is via the airway lumen into airway epithelial cells.

In anesthetized small animals, stimuli and drugs delivered directly into the airways are often given by delivery of a small volume of drug via injection into the trachea (intratracheal instillation). During inspiration, the drug is carried into the lower airways. Where the amount of drug available for use in experimental animals is limited, or where it is important to know, as closely as possible, the amount of drug that is delivered to a small experimental animal, the drug is frequently delivered by intratracheal instillation. Intratracheal instillation is an art-accepted mode of airway delivery in small animal studies, and is accepted in the field as a model of airway delivery by inhalation. Discussion of intratracheal instillation as a model of airway delivery by inhalation is provided in Sabaitis et al. ((1999) *J. Appl. Toxicol.* 19:133-140), Leong et al. ((1998) *J. Appl. Toxicol.* 18:149-160), and Ritz et al. ((1993) *Fund. Appl. Toxicol.* 21:31-37), copies of which references are provided herewith as Exhibits 1, 2, and 3, respectively. Thus, a showing of activity of a given drug by intratracheal instillation is enabling for delivery by inhalation.

Thus, Applicants have demonstrated that at least two different routes of administration – systemic and intratracheal (a model for delivery by inhalation) – are efficacious in reducing goblet cell hyperplasia. Accordingly, the specification complies with the enablement requirement of 35 U.S.C.§112, first paragraph.

Conclusion as to the rejections under 35 U.S.C.§112, first paragraph

Applicants submit that the rejections of claims 1-3, 10, 12-19, and 26 under 35 U.S.C. §112, first paragraph, have been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§112, second paragraph

Claims 1-3, 10, 12-16, and 26 were rejected under 35 U.S.C.§112, second paragraph, as allegedly indefinite.

The Office Action stated that in claim 1, lines 3-4 and in claim 26, line 2, it is unclear what is meant by the term "antagonist that binds the EGF-R to the patient."

Claim 1 is amended to recite "administering to a patient suffering from airway hypersecretion of mucus due to airway goblet cell hyperplasia an epidermal growth factor receptor (EGF-R) antagonist that binds the EGF-R." Claim 26 is amended to recite "administering to a patient suffering from nasal polyps an epidermal growth factor receptor (EGF-R) antagonist that binds an EGF-R.

The Office Action stated that in claim 26, line 2, it is unclear what is meant by "suffering nasal polyps." The above-noted amendment addresses this rejection.

Applicants submit that the rejection of claims 1-3, 10, 12-16, and 26 under 35 U.S.C.§112, second paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejections under 35 U.S.C.§102(b)

Claims 17-19 were rejected under 35 U.S.C.§102(b) as allegedly anticipated by Khetarpal. et al. ((1994) *Drug Metabolism and Disposition* 22:216-223). Claims 17-19 were rejected under 35 U.S.C.§102(b) as allegedly anticipated by Yoneda et al. ((1991) *Cancer Res.* 51:4430-4435). Claims 17-19 were rejected under 35 U.S.C.§102(b) as allegedly anticipated by Masui et al. ((1984) *Cancer Res.* 44:1002-1007). Claims 17-19 were rejected under 35 U.S.C.§102(b) as allegedly anticipated by Buchdunger et al. ((1994) *Proc. Natl. Acad. Sci. USA* 91:2334-2338).

Claims 17-19 are canceled without prejudice to renewal, thereby rendering the rejections under 35 U.S.C.§102(b) of these claims moot.

Applicants submit that the rejection of claims 17-19 under 35 U.S.C. §102(b) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

## III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCSF085CIP.

Respectfully submitted,
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Date: July 22, 2003

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